

UPDATE IN ENDOCRINOLOGY



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Open Faculty Positions:

- Director, Multidisciplinary Thyroid Center
- Academic Clinical Endocrinologists
- Academic Research Faculty

Full descriptions and contact information on back page.

CME Credit

Disclosures: Drs. Bandi, Challinor, Frahm, Helgeson, Kershaw, Korytkowski, and Mahmud report no relationships with proprietary entities producing health care goods and services.

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Dear Colleagues,

I am pleased to share our latest edition of *Update in Endocrinology!* While the mission of our Division is steadfast, we continue to grow both in knowledge and expertise to better serve the clinical and academic community.

Clinically, we continue to make great strides towards improving care of at-risk patients by providing telehealth services to patients outside the reach of quality endocrine care. In this issue, **Archana Bandi, MD**, clinical co-leader of the Endocrine Telehealth Unit and director of Telehealth Services at the Veterans Administration Pittsburgh Healthcare System (VAPHS), highlights our use of innovative telehealth programs to transform the care of rural veterans with diabetes. Our endocrine fellows, **Karla Detoya, MD**, and **Neha Karajigkar, MD**, presented the positive impact of these programs on quality and cost of diabetes care at the 2018 Annual Sessions for the Endocrine Society and American Diabetes Association, resulting in a first place award at the 2018 Endocrine Society Presidential Poster Competition.

Another way we are improving care of at-risk patients is by better understanding the impact of transitions of care and relationships on clinical outcomes. Our clinical endocrinologists **Hussain Mahmud, MD**, and **Mary Korytkowski, MD**, in collaboration with **Vicki Helgeson, PhD**, professor of Psychology at Carnegie Mellon University, discuss how these important psychosocial factors influence diabetes management across the lifespan.

Given the large endocrine catchment area of UPMC, there is never a shortage of complex cases to challenge our knowledge and expertise. In this issue, our fellow **Mihaela Oprea, MD**, and her mentor, **Sue Challinor, MD**, present an interesting case of ataxia and osteosclerotic bone lesions in a patient with a longstanding history of central diabetes insipidus. Can you guess the diagnosis?

We continue to stress the growth of our academic mission through recruitment and development of top talent. In the last interval, we welcomed two young and very talented tenure-stream assistant professors, **Sadeesh Ramakrishnan, DVM, PhD**, and **Bokai Zhu, PhD**. In this issue, we also highlight the research and career development of **Krystle Frahm, PhD**, a former postdoctoral scholar on our long-standing NIH T32 training grant, who has recently transitioned to faculty and received an NIH-funded K01 award to understand sex-dependent effects of steroid hormones on neurodevelopment, physiology, and behavior. Dr. Frahm recently received the 2018 Endocrine Society Early Investigators Award.

We also celebrate many other interval accomplishments of our faculty and trainees. **Sann Mon, MD**, was promoted to chief of Endocrinology at UPMC McKeesport, where she won the Resident Teaching Award for the third year in a row. Our clinical and research fellows presented their scholarly work at the 2018 Annual Sessions of the Endocrine Society and the American Diabetes Association, where several won awards as noted above. Likewise, several of our faculty were recently recognized as "Best Doctors," both locally and nationally. Finally, we enjoyed celebrating with our colleagues, alumni, and friends at our 2018 ADA Annual Reception in Orlando, Florida. We hope to see you at our reception next year!

If you would like to be a part of a division that rises to the challenge of providing the best of tomorrow's endocrine care today, I look forward to hearing from you!

Best wishes,



Erin E. Kershaw, MD

Chief, Division of Endocrinology and Metabolism



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UPMC LIFE CHANGING MEDICINE

Using Telehealth to Transform the Care of Rural Veterans with Diabetes

“Thanks for coordinating care for my father,” said Rachel, fighting back tears in her eyes. Rachel is a single mom and home health care nurse who had accompanied her father, Mr. Smith, to a local VA clinic in rural Pennsylvania for a video visit with an endocrinologist located over one hundred miles away at the VA Pittsburgh Healthcare System (VAPHS). Mr. Smith, a World War II veteran, was 83-years-old when his primary care provider (PCP) from James E. Van Zandt VA Medical Center in Altoona, Pennsylvania, first sought assistance from an endocrinologist for his poorly controlled diabetes. Being the sole caregiver for his elderly wife, Mr. Smith was unable to travel to Pittsburgh where the endocrinology team was located. He was, therefore, offered an initial electronic consultation and telephonic follow-up visits with an endocrinologist at the VAPHS. The endocrinology team then offered him continuity of care via clinical video teleconferencing, remote blood glucose monitoring services, and co-management of his diabetes with his PCP. This real-life story highlights the potential of emerging technologies and implementation of non-traditional collaborative care models in diabetes management.

Approximately 30.3 million people in the United States carry a diagnosis of diabetes, making it the seventh leading cause of death.¹ Concurrent with the escalating prevalence of diabetes, there is an increasing shortage of physicians and other providers who are specifically trained to care for patients with diabetes. According to the endocrinology workforce analysis commissioned by the Endocrine Society in 2012, the shortage of adult endocrinologists is expected to increase from 1,500 in 2012 to 2,700 by 2025.² Further exacerbating this problem, the 2017 National Diabetes

Statistics Report produced by the Centers for Disease Control and Prevention (CDC) indicates that diabetes is 17 percent more prevalent in rural areas compared to urban areas, and yet the majority of endocrinologists serve metropolitan rather than rural areas. Not surprisingly then, the average wait time for a non-urgent new patient visit with an endocrinologist at the time of the CDC study was 37 days. Clearly, there is a tremendous need for new models of diabetes care, particularly for patients residing in rural areas.

Telehealth has emerged as a solution for these escalating challenges. While the term telehealth and telemedicine are often used interchangeably, telehealth encompasses a wide range of health care delivery modalities, as well as health administrative options such as tumor boards and medical education. Telemedicine refers more specifically to medical care delivery processes and includes: 1) asynchronous modalities, such as remote patient monitoring (RPM) and electronic consultations (e-consults), or 2) synchronous modalities, such as virtual visits using clinical videoconferencing technology (CVT) or telephonic visits. Although telehealth implementation continues to face many challenges, patients are becoming increasingly capable of, and receptive to, these models of care. According to the fact-sheet published in February 2018 by the Pew Research Center, about three-fourths of U.S. adults own a desktop or laptop computer and nearly half own tablet devices.³ Likewise, the proportion of people who own and routinely use smartphones has risen from 35 percent in 2011 to 77 percent in 2018.³ Additionally, The Associated Press-NORC Center for Public Affairs recently conducted a survey to evaluate attitudes toward telemedicine among adults over the age of 40. This survey revealed that 88 percent of those surveyed would be comfortable using telemedicine to receive care, with a comfort level of ~87 percent for caregivers and ~50 percent for patients.⁴

In addition to the above, evidence supporting the clinical and cost effectiveness of telehealth services for diabetes is likewise growing. A systematic review of RPM of structured self-monitored blood glucoses (SMBG) and its impact on HbA1c showed that the impact was most significant when care providers incorporated specific predefined elements (spanning education, structured SMBG, and feedback) and incorporated computer decision support.⁵ RPM platforms for SMBG provide real-time support for improving quality of life (QOL), improving outcomes related to patient satisfaction, and reducing ED visits and inpatient days of care.⁶

The VAPHS has been providing telehealth diabetes services for more than a decade. The VAPHS team recently presented outcomes data at the 2018 Endocrine Society Annual Meeting and Expo⁷ in Chicago, IL and the 2018 American Diabetes Association Annual Scientific Sessions in Orlando, FL.⁸ These data demonstrate that, compared to traditional face-to-face visits, telephone-based e-consultation provides comparable reductions in A1c levels (from a baseline average of 10.1 percent to 8.9 percent at six months with sustained benefits at 12 months), but was able to do so with substantially improved access to care (27 days sooner), reduced travel distances (431 fewer miles traveled), and reduced time engaged in travel/care (9.4 hours less time).⁷ These data demonstrate the potential benefits of telehealth in diabetes care.

VAPHS is a hub location for specialty care for veterans enrolled in the western half of VISN-4 (Veterans Integrated Service Network) and serves veterans residing in upstate New York, western Pennsylvania, eastern Ohio, and adjoining West Virginia and Maryland. The majority of these veterans reside in rural areas and have a high prevalence of complex diseases, such as diabetes and obesity.



Given this acute need, the endocrinology service at the VAPHS has undergone a transformation to improve access to diabetes care for veterans closer to their homes using a variety of telehealth strategies. In addition to live, in-person consultations and follow-up care, endocrinologists at the VAPHS offer e-consults, CVT clinics, group telediabetes education, and RPM services for SMBG. Incorporation of RPM allows for safe therapy modification between appointments and for special circumstances, such as before surgical procedures, following hospital discharge, and/or during steroid use or chemotherapy. Alert guidelines for RPM for SMBG also are provided for home telehealth coordinators. Such partnerships have led to reliable care collaboration between primary care teams and hub endocrinologists.

Embedding CVT clinics as a part of the specialty care services allows for continuous care for stable yet complex needs of veterans with diabetes who live more

than 50 miles away from the hub. Currently, CVT service at the VAPHS consists of five endocrine providers (three endocrinologists and two nurse practitioners) who serve four remote hospitals and more than 15 community-based outpatient clinics. These services are available five half days per week and serve more than 120 veterans per month. Such robust partnerships led to the creation of a more specialized Insulin U-500 CVT clinic in Clarksburg, West Virginia. Complexity of care related to concentrated insulin results in a huge burden on PCPs and puts veterans at risk of medication errors, often precipitating a need for long-distance travel. For this reason, an additional two half days per month are dedicated specifically to veterans requiring Insulin U-500. In this way, endocrinologists located at the hub can provide direct care via remote teams that coordinate the visit and long-term care.

Technological advances and the innovative application of telehealth hold promise in transforming care delivery and improving

process efficiency for patients and providers alike. A well-designed telediabetes program should be nimble and have elements that serve the unique needs of the populations being served. Such programs will be increasingly necessary as the gap between the number of available endocrinologists and the patients requiring endocrine and diabetes care continues to rise.

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Psychosocial Aspects of Diabetes Management Across the Life Span

Diabetes is an incredibly challenging disease that not only affects those carrying the diagnosis, but also their family, friends, and others with whom they share close relationships. These psychosocial aspects of diabetes have the potential to dramatically influence the natural history of the disease throughout the lifespan, and yet the psychosocial factors that most strongly influence outcomes and the interventions most likely to improve these outcomes remain poorly understood.

To address these important and complex issues, UPMC endocrinologists have partnered with Vicki Helgeson, PhD, professor of psychology, and her team of investigators at Carnegie Mellon University (CMU). This collaboration arose almost two decades ago when the diabetes community recognized the multiple challenges facing youth with type 1 diabetes. Adolescence is a particularly important time to study youth with diabetes, as self-care behaviors and glycemic control have been observed to decline during this period of time. The transition through emerging adulthood is an understudied but important period, as most youth experience multiple transitions during this developmental period, including changes in lifestyle (e.g., education, occupation, living situation), changes in health care, and shifting relationships with family members, friends, and intimate others. Clinicians and investigators at UPMC and CMU realized the need to establish working relationships with experts representing the medical and psychosocial aspects of care delivery to better understand how young adults with type 1 diabetes navigate these transitions while also assuming increasing responsibility for their diabetes care and overall health.

In order to study these transitions, youth with type 1 diabetes and their nondiabetic peers were recruited and followed until age 27 in the *Teen Health* study, *Transition Times*

study, and *Research on Emerging Adults Changing Health (REACH)* study. These longitudinal studies revealed that parental involvement in diabetes was a critical determinant of self-care behavior and glycemic control during adolescence — especially for older adolescents. During emerging adulthood, the relationship with parents remained an important influence on health behaviors and psychological well-being. Higher parental support in the year after high school was associated with better adherence, fewer depressive symptoms, and lower risk behaviors among emerging adults with diabetes. In addition, parental support buffered the adverse association between peer conflict and poor glycemic control among young adults with diabetes.² When compared to healthy controls, those with diabetes did not score higher on depressive symptoms, loneliness, or bulimic symptoms, but did report lower life satisfaction and lower life purpose over time.³ An analysis of the transition from the pediatric health care system to the adult health care system showed that an early transition is associated with worse glycemic control, as well as a host of psychosocial variables (lower social status, nonwhite race, lower likelihood of pursuing college after high school graduation, and lower levels of parental involvement in their daily lives).⁴

Because individuals with diabetes are experiencing increasingly longer lifespans, it is imperative to understand how to use support resources to enhance diabetes management and quality of life in adult patients and their families. Self-management of diabetes during adulthood (involving good adherence to medication regimens and behaviors that foster good metabolic control) requires daily self-regulation of one's emotions, behaviors, and cognitions in the face of daily stressful events dealing both with one's diabetes (highs and lows in blood glucose) and other domains of life (child-rearing problems, marital conflicts, problems at work, managing other chronic illnesses). Managing daily stress occurs in the context of important social relationships, most importantly the romantic/marital

relationship. Romantic partners are likely to be most strongly affected by the person's diabetes and to most strongly influence how the person with diabetes manages his or her disease.

To study the impact of the social environment on adults with type 1 diabetes, our collaborative team embarked upon the *Diabetes Across Development In Couples (DiADIC)* study, which adopted an adult life-span perspective to examine the stressors that are linked to diabetes management and distress during young, middle-aged, and older adulthood. The focus of this study was on the ways that romantic partners may facilitate diabetes management across time through communal coping. As opposed to the pediatric and adolescent population, few studies have been performed to address how couples cope with type 1 diabetes during adulthood. The focus on communal coping involves appraisals by the persons with diabetes that the illness is shared (i.e., use of relational language such as "it is our disease" rather than an individual's disease) and collaborative coping efforts to manage the disease. The data collected through interviews, behavioral observations, and online diary assessments has allowed our investigative team to measure communal coping, diabetes management, distress, stress, and executive function. The study aim is to identify the daily stressors experienced by adults with type 1 diabetes that are linked to poorer diabetes self-management and distress, to examine the collaborative processes that are associated with better diabetes management and lower levels of distress, and to examine whether executive function abilities modulate the relation of collaborative processes to diabetes management and distress. A total of 199 couples have been recruited in this study in collaboration with the University of Utah. The investigators are currently in the midst of preparing manuscripts for publication.

A parallel study is also being conducted, titled *Communal Health Interactions in Couples (CHOICE)* study, and is looking at communal coping and diabetes management among adult couples, in which one person recently has been diagnosed with type 2 diabetes, also is being conducted. A total of 207 patients were recruited from the community who had been diagnosed with type 2 diabetes within the past five years, were married or living with a romantic partner, and whose partner did not have diabetes. The team interviewed couples in person, conducted a behavioral observation of their coping, and had them complete daily diaries for 14 consecutive days. Through all of these assessments, it was found that patients who engage in communal coping have better psychological and health behavior outcomes.^{5,6} In addition, patients who felt understood and cared for by their partners reported a better mood and were more likely to take care of themselves on a daily basis, whereas patients whose partners were identified as being more controlling on a daily basis reported poorer mood. Furthermore, patients characterized by unmitigated communion (focus on and involvement with others to the exclusion of the self) were most affected by partner supportive and unsupportive behavior.⁷ Given the increasing prevalence of type 2 diabetes in the United States and the critical role that self-care behavior plays in preventing complications, these results suggest that early intervention efforts aimed at people who are newly diagnosed with diabetes ought to target couples and

families. Intervention efforts should focus on cultivating emotional support, optimizing more subtle forms of informational support that are acceptable to patients, and minimizing controlling behaviors.

From an endocrinologist's perspective, interdisciplinary collaboration with Dr. Helgeson's team to investigate the psychosocial aspects of diabetes across the lifespan has been very enlightening. It has given collaborating clinical endocrinologists a unique perspective regarding the psychosocial needs of our patient population. This is nicely illustrated by a favorite anecdote from a patient who returned for an office visit a few months after participating in the *DiADIC* study. His hemoglobin A1c had improved by over 1 percent, which he ascribed to the interviews conducted at Dr. Helgeson's lab. He stated that the interview process made him and his wife realize that they are in this together and need to deal with his diabetes as a team. Insights gleaned from these studies will reveal novel insights into how addressing life stressors, improving coping skills, and recruiting others in key relationships with patients can improve glycemic control and diabetes outcomes among our patients. Likewise, the academic environment at UPMC is a fertile environment for multidisciplinary collaborative relationships between clinicians and researchers to create new knowledge that ultimately improves the health and well-being of our patients.

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An Interesting Case of Ataxia and Osteosclerotic Bone Lesions in a Patient with a Longstanding History of Central Diabetes Insipidus

Case Presentation

A 47-year-old male with a prior history of central diabetes insipidus (DI) presented with bone pain and ataxia.

He was initially referred to an endocrinologist in 1993 for evaluation of DI. It was concluded that he had lymphocytic infundibulitis based on the finding of a thickened pituitary stalk on MRI, while CSF examination revealed no evidence of infection or neoplastic disease. His symptoms of DI were controlled with DDAVP. He showed no other evidence of anterior pituitary hormone deficiencies. Although subsequent imaging showed resolution of the pituitary stalk thickening, his DI never resolved.

In 2012, he was admitted to the hospital for evaluation of lethargy, confusion, impaired short-term memory, and left lower extremity weakness. The altered mental status was transient and resolved five days later. A brain MRI was initially interpreted as unremarkable. A few months later, he developed progressive gait instability, slurred speech, and impaired motor coordination. He could not fully perform his work duties and lost his job. His brain MRI was reexamined and showed evidence of significant cerebellar midline atrophy. On exam, he exhibited horizontal nystagmus, dysarthria, gait impairment, and truncal ataxia greater than limb ataxia. The etiology was unclear.

He complained of chronic leg pain since 2005, which became progressively more severe. In 2018, osteosclerotic lesions were found on x-ray of his tibia, for which he underwent a bone biopsy with diagnosis of Paget's disease (PD) at a community hospital. His calcium, phosphate, 25 hydroxy vitamin D, parathyroid hormone, and alkaline phosphatase were normal.

Subsequently, he was seen at UPMC for shoulder pain. X-rays noted lesions of the pedicle of the left shoulder and pelvis, medullary sclerosis in the humeral diaphysis (Figure 1), and symmetrical lesions in the distal femur and tibia bilaterally. Bone scan and FDG-PET scan showed increased activity in the lesions. A follow-up brain MRI revealed absence of the posterior pituitary bright spot, enhancement along the proximal 7th and 8th nerve complex, disproportionate cerebellar atrophy, and enhancement along the bilateral cerebellar folia that had progressed compared to the 2012 MRI. A repeat right tibial biopsy at UPMC revealed marrow infiltration with histiocytes (some were lipid laden), fibrosis, and sclerosis of trabecular bone. The histiocytes were highlighted by CD163, CD68, CD14, factor XIIIa, and fascin. A few scattered histiocytes were BRAF V600E immunostain positive. The findings were consistent with a diagnosis of Erdheim-Chester disease (ECD). He will be treated with vemurafenib.



Figure 1. Long segment of medullary sclerosis in the right humeral diaphysis extending up to 15 cm in length corresponding with increased activity on nuclear medicine bone scan. No definite cortical thickening, periosteal reaction, erosive changes, or other aggressive features are seen. The appearance is compatible with osseous changes in Erdheim-Chester disease.

Discussion

We report a rare case of non-Langerhans cell histiocytosis originally described by Jakob Erdheim and William Chester in 1930.¹ ECD is a rare type of hematopoietic neoplasm that is characterized by abnormal proliferation and infiltration of CD68-positive, CD1a-/S100-negative foamy histiocytes causing xanthogranulomatous inflammation in multiple organs. It is not genetically inherited. Its incidence is unknown, but ~500 cases have been reported in the literature. Although described in all age groups, it is most common in adults with a mean age at diagnosis of 53 years, with a slight male predominance. The discovery of BRAF V600E mutation encountered in 50 percent of cases is proof of an oncogenic process in this disorder.² Mutations at V600E result in increased kinase activity that enhances cell proliferation and survival by activating the RAS/RAF/MEK/MAPK signaling pathway. Additional mutations in NRAS (Q61R), KRAS, ARAF, PIK3CA, and MAP2K1 have been associated with ECD.³

This disease can affect any organ system, but the most common clinical manifestation is multifocal cortical osteosclerotic lesions of the diaphyseal and metaphyseal part of long bones (95 percent). Pituitary/orbit (22 percent), central nervous system (41 percent), pulmonary (46 percent), and cardiovascular (57 percent) involvement have been reported.⁴ DI is a feature that occurs early in the disease process in ~25 percent of patients. The involvement of the pituitary commonly causes central DI, but it also can cause anterior pituitary hormone deficiencies and hyperprolactinemia.⁵ Even when there is clear evidence of radiographic regression of the pituitary disease, the endocrinopathy usually persists, as in our patient.⁶

The differential diagnosis of ECD is broad and includes Langerhans cell histiocytosis, Wegener's granulomatosis, PD, neurosarcooidosis, mycobacterial disease, and more.⁷ This patient's bone lesions were initially misdiagnosed as PD, but a repeat bone biopsy with immunostain for BRAF V600E provided his correct diagnosis. The diagnosis is best made on histopathologic evaluation of involved tissue (bone preferred) along with genetic testing or immunostaining of the tissue for BRAF V600E. The bone abnormalities seen in ECD are characterized by osteosclerotic lesions, which also are a feature in PD. In contrast to PD, the bone lesions in ECD are bilateral and symmetric, and affect the diaphysis of the long bones specifically.⁸ MRI of the brain, cardiac MRI, bone scan, and PET/CT of chest, abdomen, pelvis, and distal extremities are recommended for staging in patients with ECD.⁹

The clinical course of ECD is variable, and some patients can be asymptomatic for decades. Treatment is not necessary for patients who are asymptomatic and have no evidence of central nervous system involvement or any organ dysfunction. If symptomatic and without the BRAF V600E mutation, treatment with interferon alpha can improve survival. Glucocorticoids have been shown to have some clinical efficacy but provide no survival benefit.¹⁰ For symptomatic patients who are positive for BRAF V600E, such as our patient, the initial recommended treatment is with the BRAF inhibitor, vemurafenib, which was recently approved by the FDA for these patients.¹¹⁻¹³ Surgical debulking of large

masses and radiation therapy for palliation of bone pain can also be employed as management options.

Conclusion

In summary, we report an unusual case of a young male who initially presented with central DI associated with thickening of the pituitary stalk on MRI, and a presumed diagnosis of lymphocytic infundibulitis. More than 10 years later, he developed ataxia, bone pain, and multifocal osteosclerotic bone lesions. The bone lesions were initially misdiagnosed as PD, but a repeat bone biopsy led to the correct diagnosis of ECD, a multisystem hematopoietic neoplasm. His diagnosis was challenging due to the fact that ECD is rare and has features that overlap with other more common medical conditions.

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A Junior Faculty's Perspective on Career Development at the University of Pittsburgh

Sex-Dependent Effect of Steroid Hormones on Neurodevelopment, Physiology, and Behavior

Sex Differences in Biomedical Research

The National Institutes of Health (NIH) is the largest supporter of medical research (more than \$37 billion per year).¹ As such, the NIH is a major driver of research priorities, including increased emphasis on sex as a biological variable.² In 1993, the NIH Revitalization Act mandated the inclusion of women in clinical trials, and now women comprise half of all participants.³ This important achievement has broadened our understanding of diversity in biological responses across sexes in human research. However, not until January 2016 did the NIH extend similar consideration of sex as a biological variable to preclinical research involving cell and animal models.⁴ Proposed studies are now strongly encouraged to include both sexes or, if not, to include a legitimate scientific rationale for not doing so. Despite these recommendations, preclinical studies continue to favor evaluation of males five times more frequently than females. Even when both sexes are included, comprehensive studies are often performed in males with only confirmatory studies in females. Likewise, even if studies are powered to evaluate a particular outcome in both sexes, they are not necessarily powered to detect differences *between* the sexes. Another concern is that many investigators have not received any formal training in the proper evaluation of sex differences. Finally, evaluating both sexes increases time and cost of performing studies. Overcoming these challenges is critical for enhancing our fundamental understanding of the impact of sex on normal physiology and disease, thereby ensuring that new knowledge can be translated to both men and women.

Sex-Specific Differences in Neurodevelopment in Pre-Clinical Research

My research program focuses on sex-dependent effects of a variety of factors on early neurological development and their subsequent impact on physiology and behavior in adulthood. During my dissertation in the laboratory of Stuart A. Tobet, PhD, at Colorado State University, my research objective was to determine the sex-specific impact of glucocorticoid excess during fetal development on the development, vascularization, cellular composition, and function of specific hypothalamic nuclei.^{5,6} We found that glucocorticoid exposure had significantly different effects on male and female fetuses, including on the cellular composition and function of the blood-brain barrier in specific nuclei of the hypothalamus, as well as behavioral outcomes extending through early adulthood.

To gain further insight into the underlying mechanisms for these effects, I subsequently joined the laboratory of Donald B. DeFranco, PhD, at the University of Pittsburgh as a NIH T32-funded postdoctoral scholar. My research objective was to characterize how glucocorticoid exposure impacts gene regulation in the developing hypothalamus in a sex-specific manner, using systems-wide molecular genetic approaches.^{7,8} In doing so, we identified and characterized the sexually dimorphic dexamethasone transcriptome in mouse cerebral cortical and hypothalamic embryonic neural stem cells. The results provided insight into the mechanisms of fetal glucocorticoid exposure on hypothalamic neurodevelopment, as well as their long-term behavioral and physiological consequences in both males and females. These results also highlight the importance of sex as a biological variable in biomedical research.

These studies also have important implications for future research. Specifically, these sex-dependent effects of glucocorticoids on early neurodevelopment and subsequent physiology and behavior support the possibility of broader and more long-term effects on a variety of outcomes later in life. In particular, glucocorticoids are well known to have profound effects on energy and metabolic homeostasis, suggesting that these same processes in early development may profoundly affect risk of obesity and metabolic disease in adulthood. Researchers at the University of Pittsburgh have recently identified a novel obesity-risk variant that is highly associated with BMI and obesity risk in a specific human population.⁹ The gene harboring this variant has been shown to influence glucocorticoid receptor stability and responses to stress in preclinical models.¹⁰ Through an NIH Mentored Research Scientist Career Development Award, I am now using my background in neuroanatomy/development, neuroendocrine function, physiology and behavior, sex-differences, and systems genetics approaches to examine the impact of this gene and its risk variant on glucocorticoid receptor action within the hypothalamus in a sex-dependent manner. These studies are likely to reveal novel insights into the interaction between sex and glucocorticoid action in early development and their impact on metabolic outcomes in adulthood.

Collaborative and Supportive Research Environment at the University of Pittsburgh

During my postdoctoral training at the University of Pittsburgh, I was fortunate to be supported by a well-established institutional training program and by the NIH. I was initially recruited to the University with the support of the NIH T32 Research Training Program in Endo-

crinology, Diabetes, and Metabolism. This training grant has been in place for more than 40 years and is the longest running training grant at the University of Pittsburgh. This opportunity provided me with an instant network of experienced scientists, protected time to focus on my new research project, structure and resources to acquire new technical skills, and a rich environment to expand my knowledge. I presented my research quarterly during the Research in Progress sessions to other T32 scholars and faculty from within the Division and across the University, met with my committee annually to review my progress and future goals, and participated in grant writing and career development workshops to further my scientific development. The T32 also provided a stipend, research funds, and financial support to attend scientific meetings. This support ensured that I would devote the majority of my time to my research and career development.

I personally benefited from these established and routine interactions set up through the T32. During grant submissions, I had a network of well-established researchers who were leaders in their fields and had observed my progression from the beginning of my postdoctoral experience. I am confident that these consistent and valuable relationships provided through the T32 were instrumental in securing an NIH Loan Repayment Award, an American Diabetes Association Postdoctoral Fellowship, and an NIH Mentored Research Scientist Development (K01) Award. In addition to

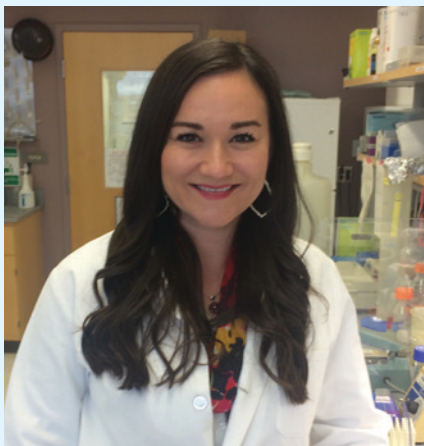
the supportive and collaborative research environment both within and outside the Division of Endocrinology and Metabolism, the University of Pittsburgh provides outstanding research infrastructure and core resources that helped drive my research and career development forward. This includes resources for genome-wide studies, DNA and protein synthesis and sequencing, animal care, proteomics, imaging, biostatistics, and metabolic studies. I continue to benefit from ongoing multidisciplinary collaborations with expert researchers in a variety of fields, including neuroscience, pharmacology, immunology, vascular medicine, bioinformatics, and genetics. Thus, the Division of Endocrinology and Metabolism at the University of Pittsburgh provides an exceptional environment for career development and research success.

I look forward to a long career tackling the most critical questions related to the impact of sex-dependent effect of steroid hormones on neurodevelopment, physiology, and behavior.

Krystle A. Frahm, PhD, is an Instructor in Medicine in the Division of Endocrinology and Metabolism at the University of Pittsburgh and is currently funded by an NIDDK Mentored Research Scientist Career Development Award. Dr. Frahm also received the Endocrine Society Early Investigator Award at the annual meeting in March 2018.

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- ⁵ Frahm KA, Handa RJ, Tobet SA. Embryonic Exposure to Dexamethasone Affects Non-Neuronal Cells in the Adult Paraventricular Nucleus of the Hypothalamus. *J Endocr Soc*. 2017 Dec 28; 2(2): 140-153.
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- ⁹ Minster RL, Hawley NL, Su C, Sun G, Kershaw EE, Cheng H, et al. A Thrifty Variant in CREBRF Strongly Influences Body Mass Index in Samoans. *Nat Genet*. 2016 Sep; 48(9): 1049-1054.
- ¹⁰ Martyn AC, Choleris E, Gillis DJ, Armstrong JN, Amor TR, McCluggage AR, Turner PV, Liang G, Cai K, Lu R. Luman/CREB3 Recruitment Factor Regulates Glucocorticoid Activity and Is Essential for Prolactin-Mediated Maternal Instinct. *Mol Cell Biol*. Dec; 32(24): 5140-50.



Krystle A. Frahm, PhD
Research Instructor in Medicine
Division of Endocrinology and Metabolism

Department News

Awards and Accomplishments



Krystle Frahm, PhD, (K01-funded Junior Faculty), under the mentorship of Erin Kershaw, MD, and Don DeFranco, PhD, received the Early Investigators Award at the 2018 Endocrine Society Annual Meeting.



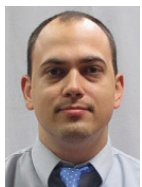
Joon Young Kim, PhD, (T32-funded Postdoctoral Scholar), under the mentorship of Silva Arslanian, MD, received the 2018 Outstanding Abstract Award at the

2018 Endocrine Society Annual Meeting for his research entitled “Metabolic Inflexibility, Impaired Lipolysis and Diminished Fat Oxidation in Obese Girls with Polycystic Ovary Syndrome (PCOS).”



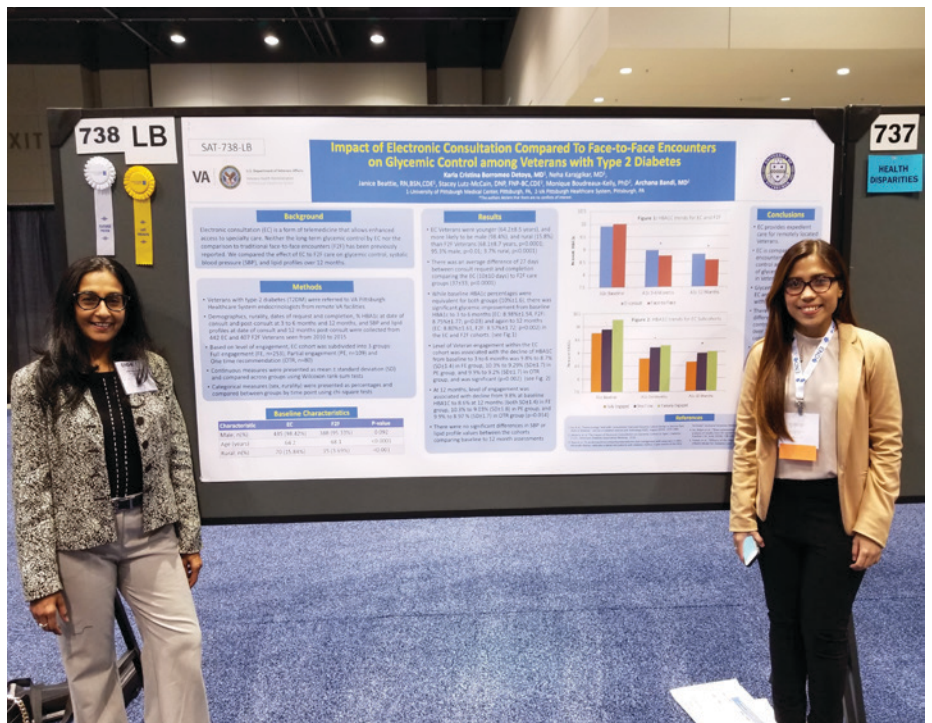
Janya Swami, MD, (Clinical Fellow), under the mentorship of Mary Korytkowski, MD, was invited to present her poster entitled “Readmission and Comprehension of

Diabetes Education at Discharge” at the 2018 Endocrine Society Annual Meeting.



Lucas Heller, MD, under the mentorship of Harsha Rao, MD, received the Young Investigator Award for Clinical Research at the 2018 VA Pittsburgh Healthcare System

Research Day for his project entitled “Glycemic Management and Mortality in Patients Undergoing CABG.” He was also invited to present this work at the 2018 American Diabetes Association 78th Scientific Sessions.



Karla Detoya, MD (Clinical Fellow) right, and **Neha Karajikar, MD** (Clinical Fellow), under the mentorship of **Archana Bandi, MD** (left) won First Place in the Presidential Poster Competition in the Healthcare Delivery and Education Category at the 2018 Endocrine Society Annual Meeting for their research entitled “Impact of Electronic Consultation Compared to Face-to-Face Encounters on Glycemic Control Among Veterans With Type 2 Diabetes.”



Hira Ali, MD, (Clinical Fellow), under the mentorship of Erin E. Kershaw, MD, and Iva Miljkovic, MD, PhD, won First Place in the postdoctoral fellow

category at the 2018 Pitt Health Disparities Research Day for her research entitled “Wny Pathway Inhibitor DKK1: A Potential Novel Biomarker for Ectopic Skeletal Muscle Adiposity.” She was also invited to present this work at the 2018 American Diabetes Association Annual Meeting. This work is supported by an Endocrine Fellows Foundation Research Grant.



Sann Yu Mon, MD, was promoted to Chief of Endocrinology at UPMC McKeesport.



Hussain Mahmud, MD, received the 2018 Dr. Frederick DeRubertis Division of Endocrinology Golden Apple Teaching Award for outstanding achievement in endocrine fellow education.



Sue Challinor, MD, **Mary Korytkowski, MD**, Shane LeBeau, MD, and Susan Greenspan, MD, were selected as *Pittsburgh Magazine's* “Best Doctors 2018.”

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Department News

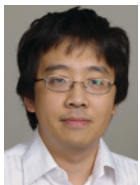
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New Faculty



Sadeesh Ramakrishnan, PhD, received his DVM at Rajiv Gandhi College of Veterinary and Animal Science and his Masters in Animal Biotechnology from the Indian Veterinary

Research Institute. He then received his PhD in Biomedical Sciences with Sonia M. Najjar, PhD, at the Center for Diabetes and Endocrine Research at the University of Toledo. He then completed his postdoctoral fellowship with Yatrik Shah, PhD, in the Department of Molecular and Integrated Physiology at the University of Michigan. His research program focuses on the role of hypoxia signaling and transcriptional regulation in normal metabolism and disease. He joined the Division of Endocrinology and the Pittsburgh Liver Research Center at the University of Pittsburgh as a tenure stream assistant professor in August of 2018.



Bokai Zhu, PhD, received his PhD in Veterinary and Biological Sciences with Jeffrey Peters, PhD, at Pennsylvania State University. He then completed his postdoctoral

fellowship with Bert O'Malley in the Department of Molecular and Cellular Biology at Baylor College of Medicine. His research program focuses on understanding the molecular mechanisms underlying circadian and non-circadian biological clocks that influence metabolism and aging. He joined the Division of Endocrinology and the Aging Institute at the University of Pittsburgh as a tenure stream assistant professor in September of 2018.



At the ADA

The UPMC Division of Endocrinology and Metabolism was once again well represented at the 2018 American Diabetes Association Scientific Sessions in Orlando, Florida. Faculty and fellows presented research findings and clinical findings, and served as invited speakers and symposia chairs. UPMC and the Division of Endocrinology and Metabolism also hosted their Second Annual UPMC Alumni and Friends Reception where colleagues and invited guests enjoyed drinks and hors d'oeuvres, and had the opportunity to network. University of Pittsburgh faculty **Thomas Songer, PhD**, **Erin Kershaw, MD**, and **Ingrid Libman DeGordon, MD, PhD**, (pictured left to right, above) were all members of the ADA Annual Sessions Organizing Committee and hosted the reception.

Notable Recent Publications

Mon SY, Riedlinger G, Abbott CE, Seeethala R, Ohori NP, Nikiforova MN, Nikiforov YE, Hodak SP. Cancer Risk and Clinicopathological Characteristics of Thyroid Nodules Harboring Thyroid-stimulating Hormone Receptor Gene Mutations. *Diagn Cytopathol*. 2018 May. 46(5):369-377.

Lutz-McCain SJ, Bandi A, Larson M. Advancing Patient Safety and Access to Concentrated Insulin (U-500 Regular Insulin) in the Veterans Health Administration: A Clinician Education Program in the Primary Care Setting. *Clin Diabetes*. 2018 Jul;36(3):244-250.

Wang J, Coleman DC, Kanter J, Ummer B, Siminerio L. Connecting Smartphone and Wearable Fitness Tracker Data with a Nationally Used Electronic Health Record System for Diabetes Education to Facilitate Behavioral Goal Monitoring in Diabetes Care: Protocol for a Pragmatic Multi-Site Randomized Trial. *JMIR Res Protoc*. 2018;7(4):e10009, DOI: 10.2196/10009, PMID: 29610111.

Wang J, Chu CF, Li C, Hayes L, Siminerio L. Diabetes Educators' Insights Regarding Connecting Mobile Phone - and Wearable Tracker - Collected Self-Monitoring Information to a Nationally-Used Electronic Health Record System for Diabetes Education: Descriptive Quality Study. *JMIR Mhealth Uhealth*. 2018; 6(7): e10206. Epub ahead of print.

OPEN FACULTY POSITIONS

Director, Multidisciplinary Thyroid Center (MTC).

The Division of Endocrinology and Metabolism at the University of Pittsburgh and its affiliated medical center, UPMC, seeks an MD or MD/PhD board-certified endocrinologist for a full-time academic faculty position as the Director of its Multidisciplinary Thyroid Center (MTC). The successful candidates should have leadership experience, strong academic expertise in thyroidology/thyroid cancer, and a desire to participate in all aspects of the academic mission (clinical care, education, and scholarly work). Candidates with research experience/interests/qualifications and potential for external funding are highly desirable.

Academic Clinical Endocrinologists. The Division of Endocrinology and Metabolism at UPMC seeks full-time BC/BE Endocrinologists to join our premier, academic, high-volume outpatient and inpatient practices. Our nationally ranked Endocrinology program provides a diverse patient mix and substantial opportunity for academic and career growth. Successful candidates will have a strong foundation in endocrinology and diabetes, and a desire to participate in all aspects of the academic mission (clinical care, education, and scholarly work). Candidates with an interest in telehealth are particularly desirable to help grow our expanding telehealth program.

Academic Research Faculty. The Division of Endocrinology and Metabolism at the University of Pittsburgh seeks MD, MD/PhD, or PhD scientists for full-time, tenure stream, academic faculty positions (assistant to full professor) in the fields of obesity, diabetes, metabolism, nutrition, and/or metabolic disease prevention. All types of research in these areas will be considered (basic, translational, clinical, epidemiological, health outcomes). Physician scientists and candidates with cross/multidisciplinary research programs are particularly desirable. Successful candidates will have a history of academic research scholarship, a strong publication record, and a demonstrated capacity to secure external research funding.

Interested candidates should send a cover letter, curriculum vitae, and contact information for three references to **Erin E. Kershaw, MD**, Chief of Endocrinology and Metabolism, care of Chelsea Dempsey (email: cad183@pitt.edu). *EEO/AA/M/F/Vets/Disabled.*

DIVISION OF ENDOCRINOLOGY AND METABOLISM

Clinical Treatment Areas:

- Diabetes
- Obesity
- Lipid Disorders
- Osteoporosis and Metabolic Bone Disorders
- Hypothalamic, Pituitary, and Adrenal Disorders
- Reproductive Hormonal Disorders
- Thyroid Disorders
- Endocrine Neoplasias

Research Areas of Focus:

- Healthy Lifestyles and Behaviors
- Diabetes Education and Management
- Type 1 Diabetes and Pancreatic Islet/Beta Cell Biology
- Type 2 Diabetes and Insulin Resistance
- Metabolic Syndrome
- Obesity, Lipodystrophies, and Adipose Tissue Disorders
- Lipid Disorders
- Muscle Metabolism and Function
- Osteoporosis and Metabolic Bone Disorders
- Thyroid Cancer Molecular Diagnosis

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To learn more about the UPMC Division of Endocrinology and Metabolism, please visit UPMCPhysicianResources.com/Endocrinology.

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A \$19 billion world-renowned health care provider and insurer, Pittsburgh-based UPMC is inventing new models of patient-centered, cost-effective, accountable care. UPMC provides more than \$900 million a year in benefits to its communities, including more care to the region's most vulnerable citizens than any other health care institution. The largest nongovernmental employer in Pennsylvania, UPMC integrates 85,000 employees, 40 hospitals, 600 doctors' offices and outpatient sites, and a 3.4 million-member Insurance Services Division, the largest medical insurer in western Pennsylvania. As UPMC works in close collaboration with the University of Pittsburgh Schools of the Health Sciences, *U.S. News & World Report* consistently ranks UPMC Presbyterian Shadyside on its annual Honor Roll of America's Best Hospitals. UPMC Enterprises functions as the innovation and commercialization arm of UPMC, and UPMC International provides hands-on health care and management services with partners around the world. For more information, go to UPMC.com.